Rejections under 35 U.S.C. §112, First Paragraph

On page 2 of the July 29, 2002 Final Office Action, the Examiner rejected claims 1, 9, 37-38, and 45 under 35 U.S.C. §112, first paragraph, written description requirement. The Examiner asserted that while the specification has described methods of causing less heightened contractility of penile and bladder smooth muscle with nucleotide sequences encoding Maxi-K and Kir6.2, the specification has not described other methods of causing less heightened contractility of smooth muscles of the urogenital tract.

In response, applicants respectfully request reconsideration and withdrawal of this ground of rejection in light of the following discussion.

Applicants assert that a description of the claimed methods is provided such that the skilled artisan would understand that the inventors had possession of the claimed invention.

Applicants direct the Examiner's attention to page 19, lines 10-26, of the specification which recite:

> The present invention specifically provides a method of gene therapy wherein the protein involved in the regulation of smooth muscle tone modulates relaxation of smooth muscle. Representative proteins which modulate relaxation include ... potassium channels (particularly the K_{ATP} and maxi-K subtypes)... . These proteins will enhance relaxation of smooth muscle, and will also decrease smooth muscle tone. In particular, where vasorelaxation is enhanced in penile smooth muscle, an erection will be more easily attained.
>
> Similarly, where smooth muscle tone is decreased in the bladder, bladder capacity will be increased. In this embodiment of the invention, the gene therapy method is particularly useful for treating individuals with bladder hyperreflexia. As used herein, a "hyperreflexic bladder" is one which contracts spontaneously so that an individual is unable to control the passage of urine. This urinary disorder is more commonly called urge incontinence, and may include urge incontinence combined with stress incontinence.

On page 27, lines 16-21, applicants teach that:

> Potassium channels are important in the regulation of human smooth muscle tone. Genes for more than thirty K^+ channels, many of which are expressed in smooth muscle, have been identified (Lawson, K., *Clinical Science*, 91:651-63, 1996; Lawson, K., *Pharmacol. Ther.*, 70(1):39-63, 1996; and Ashcroft, F.M., ed., *Ion Channels and Disease: Channelopathies*, New York: Academic Press, 2000).

Further, on page 38, lines 12-13, the specification indicates that "genetically-engineered K^+ channels ... could produce a similar desired effect." Applicants further assert that the regulation of smooth muscle tone by potassium channels is important is treating genitourinary dysfunctions (see, e.g., page 1, lines 13-17; page 6, lines 11-21; page 7, lines 12-17 and 23-27; page 8, lines 1-12; and page 17, line 16 through page 18, line 7). Thus, the application asserts that potassium channels in general, and not just K_{ATP} and maxi-K subtypes, regulate smooth muscle tone and enhance relaxation of genitourinary smooth muscle.

The Examiner asserted that it would appear from the three references referred to in the specification on page 27, line 24 through page 28, line 3 (Dorschner, *et al.*, *Mol. Pharmacol.*, 55(6):1060-66, 1999; Lee, *et al.*, *Int. J. Impotence Res.*, 11:179-88, 1999; and Benevides, *et al.*, *J. Urol.*, 161:212 (Abstract), 1999), that the K_{ATP} and maxi-K channels are the only two K^+ channels that are relevant in the context of the claimed invention. In response, applicants maintain that while these references describe multiple specific K^+ channel subtypes, the references do not teach that other K^+ channel subtypes are not also involved in enhancing relaxation of a genitourinary smooth muscle. Copies of these three references are attached hereto as **Exhibits 1-3**. Dorschner et al. (Exhibit 1) studied the effects of hypoglycemic sulfonylureas on K_{ATP} channel subtypes in transfected COS-7 cells. Lee et al. (Exhibit 2) characterized the K_{ATP} subtypes present in human corporal (penile) smooth muscle cells. Lee et al. state that "[a]mong the several

subtypes of potassium channels present in smooth muscle, the calcium-sensitive (K_{Ca}; or maxi-K channel) and K_{ATP} channel subtypes are thought to be among the most important modulators of human corporal smooth muscle tone." (Emphasis added, Int. J. Impotence Res. 11: 179-88, 1999, p. 179, right column). Thus, Lee et al. indicate that there are other important modulators of corporal smooth muscle tone besides maxi-K and K_{ATP} channel subtypes. Lee et al. go on to state that "there has been no rigorous characterization of the K^+ channel subtype(s) that might be responsible for mediating these relaxing effects of the K channel modulators/openers in human corpora. As a first step in this direction, the goal of these preliminary studies therefore, was to utilize patch clamp techniques to characterize the putative K_{ATP} channel subtype(s) ... ." (Lee et al., page 187, left column, first full paragraph.) Benevides et al. (Exhibit 3) report the effects of intracavernosal injection of a potassium channel opener on erectile dysfunction. Thus, none of the references indicated by the Examiner teach that the K_{ATP} and maxi-K channels are the only two K^+ channels that are relevant in the context of the claimed invention.

Accordingly, in view of the above discussion, applicants respectfully maintain that the claimed invention is described in the specification in sufficient detail that one skilled in the art would reasonably conclude that the inventors had possession of the claimed invention. Applicants therefore respectfully request withdrawal of this ground of rejection under 35 U.S.C. §112, first paragraph.

On page 5 of the July 29, 2002 Final Office Action, the Examiner rejected claims 1, 9, and 37-49 under 35 U.S.C. §112, first paragraph, enablement requirement.

The Examiner asserted that the claims are not enabled for methods of causing less heightened contractility in urogenital smooth muscle other than for the specific methods exemplified.

In response, applicants respectfully request reconsideration and withdrawal of this ground of rejection based on the following discussion.

Applicants first maintain that as discussed above in relation to the written description rejection, the claims are enabled for potassium channel proteins, not just for maxi-K and K_{ATP} channel subtypes. To reiterate that discussion, since the specification establishes that the claimed methods work with two separate potassium channel protein subtypes and two separate urogenital smooth muscles (see Experimental Details, page 39, line 18 through page 79, line 21), it is clear that the provision of a potassium channel is the critical step in treating heightened contractility of urogenital smooth muscle. There is no reason not to believe that another gene encoding a potassium channel could not substitute for the maxi-K gene or the K_{ATP} gene in providing a potassium channel, since methods, such as those provided in the specification, are routine for expressing a potassium channel in a smooth muscle cell. Since two separate potassium channel genes are demonstrated to provide sufficient expression in the smooth muscle cells of two separate urogenital smooth muscles, the skilled artisan would understand that there is a reasonable likelihood of success in using another potassium channel gene to enhance relaxation of genitourinary smooth muscle.

The sequences of nucleic acids encoding a variety of human potassium channel subtypes are readily available. Attached hereto as **Exhibit 4** are 19 examples of nucleic acid sequences encoding human potassium channel subtypes. It would be a matter of routine, not involving undue experimentation, for the skilled artisan to use such readily available sequences and the model systems provided by applicants (see Experimental Details, page 39, line 18 through page 79, line 21) to document additional potassium channel subtypes that enhance relaxation of genitourinary smooth muscle.

As a further comment regarding the sufficiency of applicants' examples, applicants respectfully point out that "as acknowledged by the board, examples are not *required* to

satisfy section 112, first paragraph. See, e.g. *In re Stephens*, 529 F.2d 1343, 188 USPQ 659 (CCPA 1976); *In re Borkowski*, 57 CCPA 946, 422 F.2d 904, 164 USPQ 642 (1970); In re Gay, 50 CCPA 725, 309 F.2d 769, 135 USPQ 311 (1962)." *In re Strahilevitz*, 668 F.2d 1229, 1232, 212 U.S.P.Q. 561, 563 (CCPA 1982).

The Examiner has also asserted that the specification has not provided any guidance for causing less heightened contractility of urogenital smooth muscle cells in a normal subject. In response, applicants respectfully point out that claim 1 as amended is directed to a method of enhancing relaxation of genitourinary smooth muscle in a subject having heightened contractility of the genitourinary smooth muscle. Applicants maintain that the method is enabled by the subject application.

Applicants maintain that the teachings of the specification enable the skilled artisan to practice the claimed invention without undue experimentation. Accordingly, in light of the above discussion, applicants request withdrawal of this ground of rejection under 35 U.S.C. §112, first paragraph.

On page 8 of the July 29, 2002 Final Office Action, the Examiner rejected claims 1, 9, and 37-48 under 35 U.S.C. §112, first paragraph, written description requirement, allegedly because applicants' prior amendment introduced new matter into the claims.

In response, applicants maintain that support for claim 1 as amended can be found in the specification on page 1, lines 13-17; page 3, lines 9-14; page 5, line 28 through page 6, line 1; page 6, lines 11-21; page 7, lines 12-17 and 23-27; page 8, lines 1-12; page 17, line 16 through page 18, line 7; page 19, lines 10-26; page 27, lines 6-7, 10-11, and 16-18; page 38, lines 12-13; and in the Experimental Details, page 39, line 18 through page 79, line 21.

Conclusion

In light of the claim amendments and the above remarks, applicants respectfully request withdrawal of all rejections and passage of the claims to allowance. If there are any minor matters that would prevent allowance of the claims, applicants request that Examiner Paras contact the undersigned attorney.

No fee is deemed necessary in connection with the filing of this Amendment. However, if there are any unanticipated fees required to maintain the pendency of this application, the PTO is authorized to withdraw those fees from Deposit Account 01-1785. Overcharges may also be credited to Deposit Account 01-1785.

Respectfully submitted,
AMSTER, ROTHSTEIN & EBENSTEIN
Attorneys for Applicant
90 Park Avenue
New York, New York 10016
(212) 697-5995

Dated: New York, New York
October 29, 2002

By: _____
Craig J. Arnold
Registration No.: 34,287
Alan D. Miller
Registration No.: 42,889

Marked-up Claims After Amendment - U.S. Patent Application No. 09/531,969
Additions are underlined, deletions are bracketed

1. (Three times amended) A method of [causing less] enhancing relaxation of a genitourinary smooth muscle in a subject having heightened contractility of [a] the genitourinary smooth muscle [in a urogenital tract of a subject], comprising the direct introduction and expression of a DNA sequence encoding a potassium channel protein which enhances relaxation of the genitourinary smooth muscle, in a sufficient number of the genitourinary smooth muscle cells [of the urogenital tract] of the subject to enhance relaxation of the genitourinary smooth muscle in the subject [result in less heightened contractility of the smooth muscle in the urogenital tract of the subject].

9. The method of Claim 1, wherein the potassium channel protein is maxi-K or K_{ATP}.

37. The method of Claim 1, wherein the smooth muscle cells are penile smooth muscle cells.

38. The method of Claim 1, wherein the smooth muscle cells are bladder smooth muscle cells.

39. The method of Claim 1, wherein the potassium channel protein is maxi-K.

40. The method of Claim 1, wherein the potassium channel protein is K_{ATP}.

41. The method of Claim 37, wherein the potassium channel protein is maxi-K.

42. The method of Claim 37, wherein the potassium channel protein is K_{ATP}.

43. The method of Claim 38, wherein the potassium channel protein is maxi-K.

44. The method of Claim 38, wherein the potassium channel protein is K_{ATP}.

45. The method of Claim 1, wherein the DNA sequence is introduced by naked DNA transfer.

46. The method of Claim 41, wherein the DNA sequence is introduced by naked DNA transfer.

47. The method of Claim 42, wherein the DNA sequence is introduced by naked DNA transfer.

48. The method of Claim 43, wherein the DNA sequence is introduced by naked DNA transfer.

49. The method of Claim 44, wherein the DNA sequence is introduced by naked DNA transfer.